

**MEASURING IMPAIRMENT:
VALIDATED METHODS FOR ASSESSING
SEDATING MEDICATIONS**

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*FDA/NTSB PUBLIC HEARING: Transportation Safety and Potentially
Sedating or Impairing Medications, November 14-15, 2001, Washington, DC*

**Attitudes & Use of Sedating
OTC Medications**

- Public shows little awareness of the risks of using common sedating OTC medications
- Public believes that if you aren't drowsy you aren't sedated

Definition of Sedation

- Depression of brain functioning by a medication, manifested by:
 - sleepiness, drowsiness, fatigue
 - slowed brain activity
 - reduced wakefulness
 - impaired performance

Methods for Evaluating Sedation

- Self-report measures
- Physiologic measures
- Performance measures

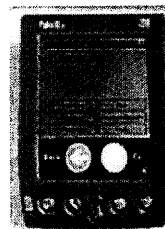
**Evaluating Sedation:
Self-Report Methods**

- ☐ Diary Cards
- ☐ Rating Scales, Mood Inventories
- ☐ Visual Analog Scales
- ☐ Personal Data Assistant (e.g., Palm Pilot)
- ☐ Prescription Event Monitoring

**Real-Time Measurement of Personal
Experience**

- High subject compliance
- Time-logging of entries
- Improved data handling

Superiority to paper diary
demonstrated in recent
SUNY study (Shifman et
al., 2001)



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Limitations of Self-Report Measures

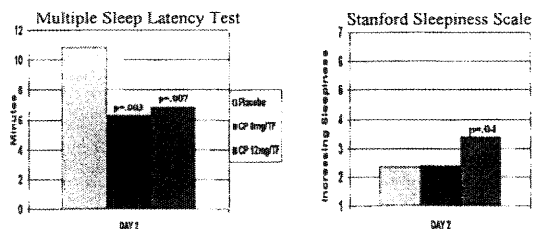
- Subjectivity
- Biased reporting
- Poor diary compliance
- Low agreement with physiological and performance measures
 - self-reported sleepiness fails to reflect physiological sleepiness¹
 - self-reported sleepiness fails to reflect cognitive performance deficit²
 - self-reported sleepiness fails to reflect driving performance³

1. Kay GG, Plotkin KE, Quig MB, et al. *Am J Man Care*. 1997;3:1843-1848.
 2. Yaxouda S, Zannikos P, Kay G, et al (submitted for publication; Nov 2001)
 3. Weiler JM, Bloomfield JR, Woodworth GG, et al. *Ann Intern Med*. 2000;132:354-63.

Evaluating Sedation: Physiologic Measures

- EEG (e.g., continuous EEG for microsleeps)
- Evoked potentials (e.g., P300)
- Functional brain imaging (e.g., PET and fMRI)
- Multiple sleep latency test (MSLT)
- Activity monitors (e.g., wrist actigraph)

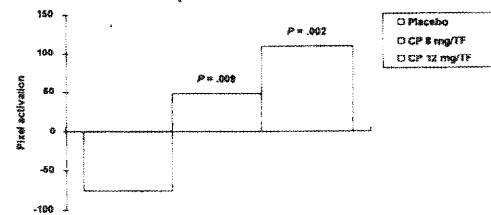
Effect of Evening Chlorpheniramine and Morning Terfenadine (AM/PM Dosing)



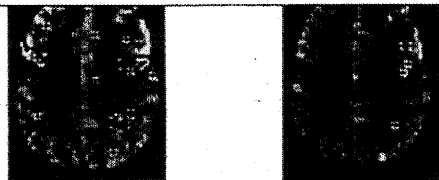
1. Kay GG, Plotkin KE, Quig MB, et al. *Am J Man Care*. 1997;3:1843-1848

Functional MRI: Mental Arithmetic Test

Change From Baseline to Day 3 of AM-PM Dosing: Frontoparietal Brain Activation



Starbuck et al. *Human Psychopharmacology*. 2000



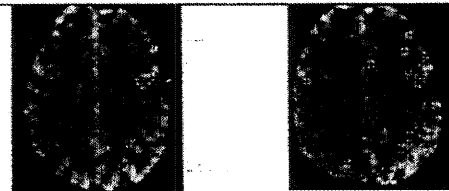
PHASE 1

Location: Left/Right Frontal Left/Right Parietal
 Frontal: Left/Right
 Parietal: Left/Right

PHASE 2

(Placebo)

Starbuck et al. *Human Psychopharmacology*. 2000



PHASE 1

Location: Left/Right Frontal Left/Right Parietal
 Frontal: Left/Right
 Parietal: Left/Right

PHASE 2

Chlorpheniramine 12 mg

Starbuck et al. *Human Psychopharmacology*. 2000

Evaluating Sedation: Performance Measures

- Cognitive testing
- Psychomotor testing
- Simulation (e.g., driving, flying)

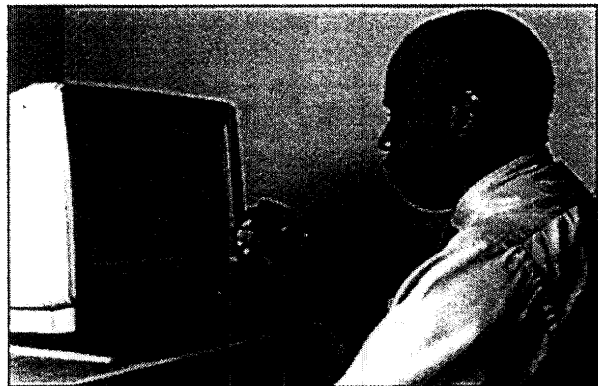
Characteristics of Computerized Neuropsychological Tests

- Standardized instructions and stimulus presentation
- Enhanced sensitivity to detect neuro-cognitive and psychomotor changes
- Highly accurate measurement of speed and accuracy
- Designed for repeated administration
- Predictive of performance of real-world activities (e.g., flying)

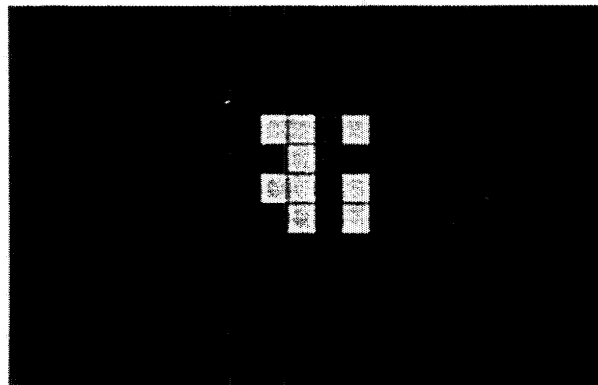
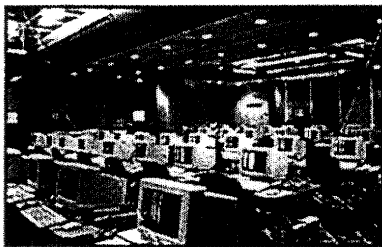
Kane & Kay, Neuropsychology Reviews, 1997

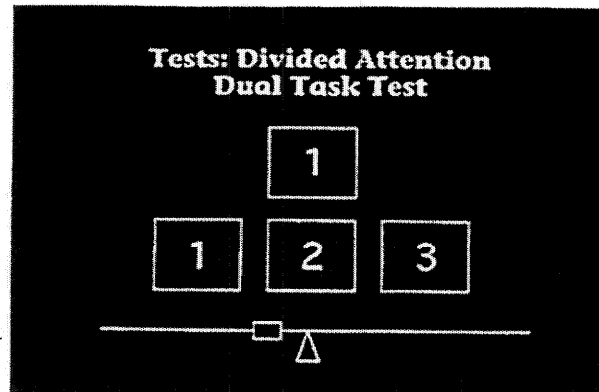
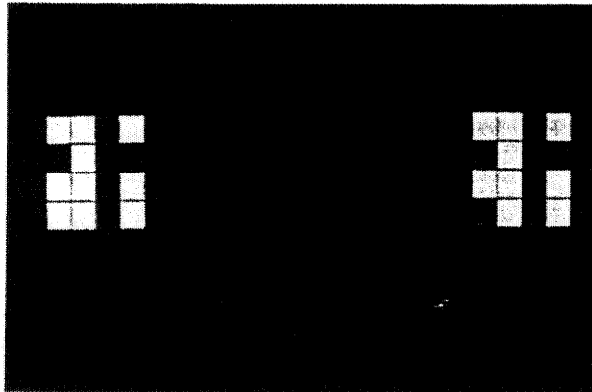
PHARMACEUTICAL RESEARCH EMPLOYING CogScreen®

- ANTIHISTAMINES (DOD, FDA, Pharma)
- ANTIHYPERTENSIVES (FAA)
- NUTRASWEET (FAA/FDA)
- CHOLESTEROL LOWERING MEDICATIONS (Pharma)
- ORAL DIABETES MEDICATION (Pharma)
- HORMONE REPLACEMENT THERAPY (Pharma)
- ANTIBIOTICS (Pharma)



Computerized Neuropsychological Testing of Performance



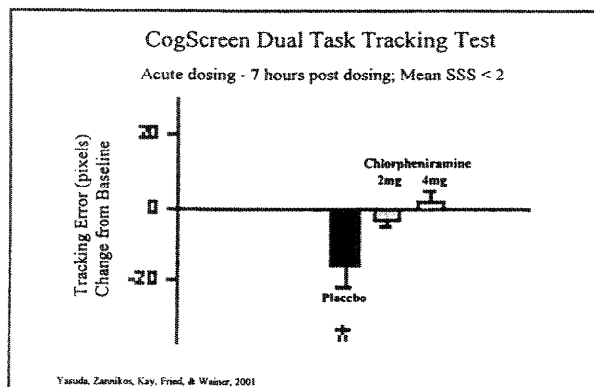
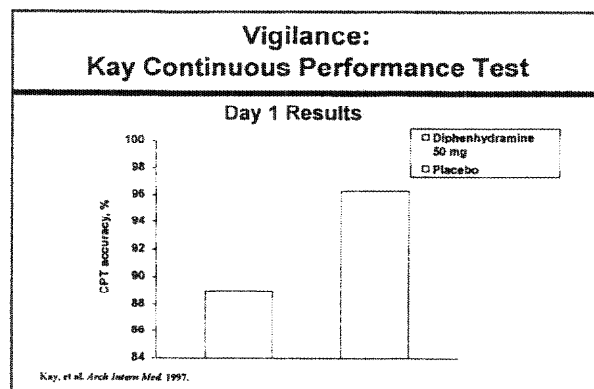


CRITICAL COGNITIVE DOMAINS FOR DEMONSTRATING SEDATION

VIGILANCE: Capacity to sustain attention under conditions of minimal arousal (e.g., monotonous tasks)

DIVIDED ATTENTION: Ability to perform simultaneous mental activities (especially tracking)

WORKING MEMORY: Ability to hold information temporarily in one's head for purposes of using the information in a calculation, or other mental activity



Summary

- Sedating medications can cause impairment in the absence of sleepiness.
- Sedating effects may carry over to the following day even when medications are taken at night.
- Functions most vulnerable to sedating medications are: vigilance, psychomotor skills under divided attention conditions, and working memory.
- Reliable and valid measures are currently available for evaluating the self-report, physiological and performance effects of medications.